



Connectomics at cellular precision

Introduction

While the analysis of long-range neuronal projections using non-invasive imaging techniques is already broadly established (see also the contributions by Hilgetag and Ritter in this issue of *Neuroforum*), the dense mapping of neuronal connections at the level of single synapses and nerve cells is still in its infancy. One cubic millimeter of nerve tissue (i. e. a typical voxel in macroscopic non-invasive imaging) contains about 100,000 nerve cells and about 1 billion chemical synapses, e. g. in the grey matter of mammalian cerebral cortex. The mapping of even just one of such volumes at a resolution required for dense circuit mapping (about $[10 \times 10 \times 30] \text{ nm}^3$) has not been achieved yet and is far from being a routine method. In fact, such a single voxel in magnetic resonance imaging (MRI)-based connectomics corresponds to a dataset of a third of a petabyte in electron microscopy (EM)-based (connectomics). This illustrates the magnitude of the technological challenges that cellular connectomics is facing today [11].

The imaging methods and data analysis approaches in cellular connectomics have been described here before [12]. The following shall briefly summarize the novel neuroscientific insights that have been recently obtained, followed by a description of the most pressing research questions in this field.

Network structure and brain function

While other research areas, namely protein biology, have naturally embraced the relevance of structural data for a detailed understanding, and structural measure-

ments are the standard method in these fields, the question whether structural information about nerve cell networks can provide insights about the function of nervous systems is still open and urgent. Especially since substantial methodological efforts and substantial resources have to be invested for complete circuit mapping in cellular connectomics, the purpose of such research is still highly disputed and questioned (see for instance [2, 8]). The following shall briefly summarize the so far obtained scientific evidence for the inference of functional insights from nerve cell network structure and indicate where such evidence is still missing.

Connectomics in the sensory periphery

The primary success of cellular connectomics has been the clarification of how directional signals are computed in the visual system of the fly and the mammalian retina. Already more than 50 years ago, Barlow and Levick [3] discovered that certain types of ganglion cells in the retina selectively respond to directed motion in the visual field (“direction selectivity”). Ever since, numerous theoretical and experimental studies have been conducted to elucidate such specific functional selectivity. Is this functional phenomenon implemented by specific nerve cell connections or rather an effect of subtle modifications of synapse strength — or other “dynamic” computational processes? The answer to these questions is rather clear by now: Direction selectivity in the mammalian retina is first encoded in certain amacrine cells; then these amacrine cells transmit the direction selectivity highly specifically to the corresponding gan-

glion cells via specific targeted synaptic wiring. This is the mechanism by which the ganglion cells obtain their direction selectivity [7]. The specificity of this innervation is even operating at the level of single dendrites of the amacrine cells (thus highly selectively) and the synaptic imbalance is about 13 fold (i. e. about 13 times more synapses are established in the computationally appropriate direction than in the inverse direction).

The origin of direction selectivity in the amacrine cells has also been studied, and in the meantime substantial evidence has been found that this computation is also implemented via targeted neuronal wiring [10, 16]. A recently published study was even able to show that depending on the size of the animals’ eyes and thus their retinæ, different species adapt the neuronal wiring responsible for the direction selectivity computation in order to be able to optimally respond to the movement velocities of visual signals on their respective retina [10].

Thus it is beyond any doubt that in the sensory periphery of the mammalian nervous system the opportunities of implementing neuronal computations via connectomic specificities is extensively made use of. Most interestingly, analyses in the visual system of the fruit fly have provided evidence that comparable connectomic principles are being used in the circuits of this rather evolutionarily distant animal [22]. However, the precise identity of the neurons involved is still controversial ([19, 22]; see also [5] for an extended discussion).

The connectome of the optical system of insects and the visual periphery of mammals can thus be considered clear evidence that in these systems specific nerve cell connections are used to im-

plement the algorithms relevant for the animal's behavior.

Cellular connectomics of the cerebral cortex

What's the status of cellular connectomics of the mammalian cerebral cortex? This part of the mammalian brain contains about 16 bn nerve cells [1] and about 160 trillion chemical synapses in the human brain (these numbers are about 1000 fold less in the mouse brain). Connectomic studies of the cerebral cortex thus require the analysis of substantial tissue volumes which are so far resisting extensive connectomic mapping because of the highly non-local wiring of every single cortical nerve cell.

But is connectomic analysis in the cerebral cortex worth the effort? A simple analogy based on the insights from the mammalian retina is dangerous — as much as the fact that connectomes may have been of limited value in the worm *C. elegans* or the stomatogastric ganglion of the lobster did not allow conclusions about the relevance of connectomes in the visual systems of fly and mouse.

Whether the structure of nerve cell networks in the cerebral cortex is essential for concrete neuronal computations and at which precision are open questions. Connectomic studies in the cerebral cortex have so far been carried out in tissue blocks of only about 50–70 micrometer thickness [4, 17]. This size limitation also limited the possible insights about the precision of network architecture in cortex. The recently published, first locally dense reconstruction from mouse cortex [15] was limited to about $10 \times 10 \times 30$ cubic micrometers tissue volume. This data was able to enforce evidence that the direct touch of nerve cells has only limited predictive value for the existence of chemical synapses between these nerve cells (see also [21]). The question whether pairwise random connectivity dominates also at the level of entire axons and nerve cells (so-called “Peter's rule”, [6]) or whether highly specific nerve cell networks are being established in the cerebral cortex has thus still to be considered unanswered.

Interestingly, theoretical studies have shown that even mostly randomly wired circuits allow relevant computations [18] and can generate structured maps as representations of the sensory world [14]. Whether the mammalian cerebral cortex is operating in such a random connectivity regime or is rather using precise connections as in the sensory periphery is a major open scientific question.

Substantial research efforts are undertaken to systematically map connectomes in the cerebral cortex. An important focus is on comparative connectomic analysis—fueled by the notion that such comparative mapping can provide insights into circuit invariances and structural principles (see [13] for a summary). The mapping and analysis of cortical connectomes is receiving substantial funding in the US by the research initiative of the intelligence agencies IARPA [20] — also driven by the hope that algorithmic insights for improved machine-based data analysis could be gained from analyzing the circuits in mammalian brains. The new DFG priority program Computational Connectomics [9] is now providing appropriate support at least for the theoretical analysis of connectomic data in Germany—which should now be put to use.

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Abstract

The complete mapping of neuronal circuits in at least parts of brains has received substantial attention recently. Methodological breakthroughs have made the imaging of ever larger tissue blocks realistic using 3-dimensional electron microscopy. Analysis of such data, however, is still limiting the neuroscientific insights obtainable from cellular connectomics data. What is the state of this scientific field, which insights have been obtained, which are in reach? This brief overview summarizes the current knowledge in cellular connectomics.

Keywords

Connectomics · Electron microscopy · Cerebral cortex · Neuronal circuits

Compliance with ethical guidelines

Conflict of interest. M. Helmstaedter declares that he has no competing interest.

This article does not contain any studies with human participants or animals performed by the author.

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